where despite the mutation, they can function. This invention has practical applications in treating or curing any disorder or disease which directly or indirectly results from mis-folded ER proteins including, but not limited to, clinical conditions related to the misfolding and/or non-release of the transmembrane precursors of the glycosylphosphatidylinositol-linked proteins, low density lipoprotein receptor, the thyroid prohormone thyroglobulin (Tg), Class I histocompatibility proteins as occurs in tumors and in numerous viral infections, as well as CFTR and α-antitrypsin.

While many groups are currently trying to overcome these types of diseases and clinical conditions through gene therapy, the approach of the present invention employs chemical pharmaceuticals to rescue the endogenous mutant protein. It is likely, therefore that our method will not be limited by the current challenges which confront gene therapy efforts, including low multiplicity of transformation, low levels of expression, and inflammation and immune responses to the requisite viral vectors. Recent deaths associated with experimental gene therapies further indicate the need for alternative treatment methods. Our approach is also the first to attempt to defeat ER retention of mis-folded proteins by interfering directly with ER quality control mechanisms.

As described in detail herein, this invention encompasses various compositions and methods which reduce the activity of any ER chaperone including, but not limited to, UGGT and thereby permit exiting of mis-folded and mis-assembled proteins from the ER. Such compositions include compounds which covalently bond to modified UGGT and irreversibly inhibit its catalytic function. Exposure to oligonucleotides whose sequences are antisense to the UGGT coding sequence will also reduce UGGT expression and activity. Optimal UGGT activity requires high concentrations of Ca^{2+}. Our research also demonstrates that interfering with UGGT activity by depleting ER Ca^{2+} stores through various treatments, such as with calcium pump inhibitors, allows the mis-folded but functional ΔF508 CFTR protein to "escape" from the ER and reach the cell surface. Thus, our discovery also provides novel and clinically applicable treatment for reversing or preventing diseases or clinical conditions which result from the ER-associated retention or degradation of mis-assembled or mis-folded glycoproteins.

SUMMARY OF THE INVENTION

This invention provides methods and reagents for treating any disease or clinical condition by administering an agent that permits the release of proteins from the ER. More particularly, this invention provides such methods wherein the disease or clinical condition

is at least partly the result of endoplasmic reticulum-associated retention or degradation of mis-assembled or mis-folded proteins.

In one embodiment of the invention, methods are provided wherein the agent permits release of mis-assembled or mis-folded proteins from the endoplasmic reticulum. Preferably the mis-assembled or mis-folded proteins retain sufficient activity to relieve at least some of the symptoms of the disease or clinical condition.

In another embodiment of the invention, methods are provided wherein the proteins being released are glycoproteins.

The methods of the present invention are useful for treating diseases or clinical conditions such as Cystic Fibrosis, Chronic Obstructive Pulmonary Disease, Paroxysmal Nocturnal Hemoglobinuria, Familial Hypercholesterolemia, Tay-Sachs Disease, viral diseases, neoplastic diseases, Hereditary Myeloperoxidase Deficiency, Congenital Insulin Resistance, Rhinosinusitis, Hemochromatosis, Gitelman's Syndrome, Cystinuria, and certain forms of Nephrogenic Diabetes Insipidus.

In one embodiment of the invention, the methods involve using agents which act as calcium pump inhibitors.

In another embodiment of the invention, the methods involve using agents which decrease or inhibit the functional activity of UDP glucose:glycoprotein glycosyl transferase.

In still another embodiment of the invention, the methods involve using agents that decrease or inhibit activity of the endoplasmic reticulum Ca^{++} ATPase.

In yet another embodiment of the invention, the methods involve using agents that lower the concentration of Ca^{++} in the endoplasmic reticulum.

In another embodiment of the invention, the methods involve using agents that cause release of Ca^{++} from the endoplasmic reticulum.

In yet another embodiment of the invention, the methods involve using agents that increase or stimulate IP_3 receptor activity.

In yet another embodiment of the invention, the methods involve using agents that increase or stimulate ryanodine receptor activity.

In still another embodiment of the invention, the methods involve using agents that decrease or inhibit calnexin functional activity.

Examples of agents which are useful in the methods of the present invention include, but are not limited to, thapsigargin or a derivative thereof, cyclopiazonic acid or a derivative thereof, DBHQ or a derivative thereof, or halothane or a derivative thereof.

Additional examples of agents that are useful in the methods of the present invention include, but are not limited to, oligonucleotides which are antisense to UDP glucose:glycoprotein glycosyl transferase, calnexin or Ca^{++} ATPase.

The present invention also provides methods wherein the agents are administered to the pulmonary system, such as by using an aerosol.

The present invention provides methods of releasing a mis-assembled or mis-folded glycoprotein from the endoplasmic reticulum of a cell by administering an agent that decreases or inhibits the functional activity of UDP glucose:glycoprotein glycosyl transferase.

The present invention also provides methods of releasing a mis-assembled or mis-folded glycoprotein from the endoplasmic reticulum of a cell by administering an agent that decreases or inhibits activity of the endoplasmic reticulum Ca^{++} ATPase.

The present invention also provides methods of releasing a mis-assembled or mis-folded glycoprotein from the endoplasmic reticulum of a cell by administering an agent that lowers the concentration of Ca^{++} in the endoplasmic reticulum.

The present invention also provides methods of releasing a mis-assembled or mis-folded glycoprotein from the endoplasmic reticulum of a cell by administering an agent that decreases or inhibits calnexin functional activity.

The present invention also provides methods of increasing the permeability of the apical surfaces of airway epithelial cells to a chloride ion by administering an agent that decreases or inhibits the intracellular retention of mis-assembled or mis-folded glycoproteins.

The present invention further provides methods of increasing the permeability of the apical surfaces of airway epithelial cells to a chloride ion by administering an agent that decreases or inhibits the activity of UDP glucose:glycoprotein glycosyl transferase.

The present invention also provides methods of increasing the permeability of the apical surfaces of airway epithelial cells to a chloride ion by administering an agent that decreases or inhibits activity of the endoplasmic reticulum Ca^{++} ATPase.

The present invention further provides methods of increasing the permeability of the apical surfaces of airway epithelial cells to a chloride ion by administering an agent that lowers the concentration of Ca^{++} in the endoplasmic reticulum.

The present invention also provides methods of increasing the permeability of the apical surfaces of airway epithelial cells to a chloride ion by administering an agent that decreases or inhibits calnexin functional activity.